Notch post-translationally regulates beta-catenin protein in stem and progenitor cells.

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Public Summary:
Cells make decisions about how to reproduce or develop into specialized cell types according to a complex network of proteins that send signals instructing cells to perform different tasks at various time points in their development. Two of these pathways, Notch and beta-catenin, contribute to the regulation of cell growth and fetal development. We found that when Notch interacts with beta-catenin, it results in the degradation of beta-catenin, which in turn regulates the growth of both stem cells and cancer cells. Conversely, when Notch and beta-catenin don't interact, stem cells expand out of control. Disruption of the balance of these two proteins can lead to a malformed heart during embryonic development.

Scientific Abstract:
Cellular decisions of self-renewal or differentiation arise from integration and reciprocal titration of numerous regulatory networks. Notch and Wnt/beta-catenin signalling often intersect in stem and progenitor cells and regulate each other transcriptionally. The biological outcome of signalling through each pathway often depends on the context and timing as cells progress through stages of differentiation. Here, we show that membrane-bound Notch physically associates with unphosphorylated (active) beta-catenin in stem and colon cancer cells and negatively regulates post-translational accumulation of active beta-catenin protein. Notch-dependent regulation of beta-catenin protein did not require ligand-dependent membrane cleavage of Notch or the glycogen synthase kinase-3beta-dependent activity of the beta-catenin destruction complex. It did, however, require the endocytic adaptor protein Numb and lysosomal activity. This study reveals a previously unrecognized function of Notch in negatively titrating active beta-catenin protein levels in stem and progenitor cells.